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(21) International Application Number: PCT/IB98/00662 (22) International Filing Date: 1 May 1998 (01.05.98) (30) Priority Data: 60/045,635 5 May 1997 (05.05.97) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LUNDY, Kristin, Marie [US/US]; Apartment 631, 600 Meridian Street, Groton, CT 06340 (US). RICKETTS, Anthony, Paul [GB/US]; 1306 Pequot Trail, Stonington, CT 06378 (US). (74) Agents: SPIEGEL, Allen, J.; c/o Mark Charles Green, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COX-2 SELECTIVE CARPROFEN FOR TREATING PAIN AND INFLAMMATION IN DOGS (57) Abstract Treating or preventing inflammatory processes and diseases in dogs associated with the activity of inducible cyclo-oxygenase-2 (COX-2), while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on <i>ex vivo</i> inhibition levels measured in whole blood; the inhibitor is a member selected from the group of anti-inflammatory compounds consisting essentially of salicylic acid derivatives, <i>p</i> -aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, and alkanones; the inhibitor in particular is comprised of (+)/ <i>S</i> -enantiomer of 6-chloro- α -methyl-9 <i>H</i> -carbazole-2-acetic acid.		

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providing delayed-, sustained-, and/or controlled-release of said inhibitor; (b) contained in a particulate composition which is inhaled into the lungs; or (c) contained in a particulate composition which is blown into suitable body tissues or cavities, where said composition optionally provides delayed-, sustained-, and/or controlled-release of said inhibitor; or (4) ingestion of a pharmaceutical composition containing said inhibitor in suitable solid or liquid form for peroral delivery of said inhibitor, where said inhibitor is: (a) contained in a solid dosage form; or (b) contained in a liquid dosage form. Suppositories may be regarded as a special type of implant, since they comprise bases which are solid at room temperature but melt at body temperature, slowly releasing the active ingredient with which they are impregnated into the surrounding tissue of the body, where the active ingredient becomes absorbed and transported to effect systemic administration. Dosage forms which permit transdermal and transmucosal administration to achieve systemic delivery are also contemplated, especially including transdermal patch technology.

There is further provided the above-described method of treating or preventing pain and inflammation comprising ingestion or administration of a solid peroral dosage form selected from the group consisting of delayed-release oral tablet, capsule, caplet, lozenge, troche, and multiparticulates, enteric-coated tablets and capsules which prevent release and absorption in the stomach to facilitate delivery distal to the stomach of the dog, sustained-release oral tablets, capsules and microparticulates which provide systemic delivery of the active ingredient in a controlled manner over at least a 10-hour period, a fast-dissolving tablet, encapsulated solutions, an oral paste, a granular form incorporated in or to be incorporated in the food of the dog being treated, and a chewable form in which said active ingredient is consumed along with the palatable chew, or may alternatively be delivered by leaching from the body of the chew which is not consumed, during mastication by the dog being treated. Also included for use with the above-described dosage forms are microencapsulated formulations of the active ingredient, which may then be incorporated into a tablet, capsule, or other final formulation. Still further, there is provided said method comprising ingestion of a liquid peroral dosage form selected from the group consisting of a solution, suspension, emulsion, inverse emulsion, elixir, extract, tincture, and concentrate, optionally to be added to the drinking water of the dog being treated. Any of these liquid dosage forms, when formulated in accordance with methods well known in the art, can either be administered directly to the dog being treated, or may be added to the drinking water of the dog being treated. The concentrate liquid form, on the other hand, is formulated to be added first to a given amount of water, from which an aliquot amount may be withdrawn for administration directly to the dog or addition to the drinking water of the dog.

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when administered in systemic or local, oral or parenteral applications and for this purpose are combined with the usual pharmaceutical excipients, diluents and adjuvants, e.g., organic and inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols, etc. These pharmaceutical preparations can be employed in a solid form, e.g., as tablets, troches, suppositories, capsules, and especially in combination with or for admixture with a palatable food item suitable for dogs; or they can be administered in liquid form, e.g., as solutions, suspensions, standard and inverse emulsions, and elixirs. Pharmaceutical excipients and adjuvants which can be added include preservatives, antioxidants, antimicrobial agents and other stabilizers; wetting, emulsifying, and suspending agents, and anticaking compounds; fragrance and coloring additives; compositions for improving compressibility, or to create a delayed-, sustained-, or controlled-release of the active ingredient; and various salts to change the osmotic pressure of the pharmaceutical preparation or to act as buffers. Particular dosage forms which have been used with success include a 5% mixed-micelle solution of carprofen for intravenous injection, a 3% palatable paste, and oral tablets in 25 mg, 75 mg, and 100 mg dosages.

In the methods and compositions of the present invention, especially those wherein the inhibitor comprises 6-chloro- α -methyl-9H-carbazole-2-acetic acid and both resulting enantiomers are present together, it is a preferred embodiment to use a non-racemic mixture. Particularly, in such preferred non-racemic mixtures, it is desirable to have the (+)(S) enantiomer present in amount of at least 85%, preferably at least 90%, more preferably at least 95%, and most preferably at least 99%. Thus, in such non-racemic mixtures the (+)(S) enantiomer will be the predominant component, not only because it is significantly more potent than the (-)(R) enantiomer in inhibiting cyclo-oxygenase-2 (COX-2), but also because it is highly selective with respect to inhibiting cyclo-oxygenase-2 (COX-2) as compared to cyclo-oxygenase-1 (COX-1). The correspondingly smaller amounts of the (-)(R) enantiomer, i.e., less than 15%, less than 10% and less than 5%, respectively, are optionally included where a balance of cyclo-oxygenase or other enzyme inhibitory properties is deemed desirable. Where the amount of (-)(R) enantiomer present is less than 5% and less than 1%, the reason for the inclusion will usually reflect the practicalities of the method used to resolve the enantiomers. Where this method is time consuming or demanding of resources, it will often be desirable, from a practical standpoint, to simply allow this smaller proportion of the (-)(R) enantiomer to be carried over into the final, non-racemic mixture final product.

The anti-inflammatory inhibitors of Formula (I) of the present invention may be administered systemically to a dog to be treated as a pharmaceutical composition in suitable